Maternal–fetal heartbeat phase synchronization

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Integrated physiological systems under neural control, such as the cardiac and respiratory systems, exhibit complex dynamics with continuous noisy fluctuations even in resting "equilibrium" conditions without external perturbations (1, 2). Advances in analytic methods have made it possible to identify a surprisingly robust temporal organization embedded in physiologic fluctuations, characterized by scale-invariant (fractal), multifractal, and nonlinear features over a range of time scales (2–4). This behavior is remarkably different from the one postulated by the classical principle of homeostasis (5), and it resembles the dynamics of certain physical systems away from equilibrium (6).

Although the origins of such rich complexity in physiologic fluctuations remain poorly understood, there is growing evidence that they are related to particular mechanisms of regulation involving networks of multiple inputs and nonlinear feedback interactions (7), as various aspects of their temporal organization change with different physiological states (8, 9) and pathological conditions (2, 4, 10). This picture is further complicated by nonlinear interactions between physiologic systems, where the specific mechanism of their coupling is often masked by physiologic fluctuations, as in the case of maternal–fetal cardiac interaction.

The fetal heart rate, a primary accessible indicator of prenatal development, changes with the physiological and psychological state of the mother: fetal heart rate variability and body movement substantially decrease with hypooxygenation of maternal arterial blood (11); increased maternal stress and anxiety levels correlate with increased mean fetal heart rate (12); during the night the mean hourly fetal heart rate decreases in synchrony with the mean maternal heart rate (13). This correlated behavior in the mean heart rates suggests certain coupling between the cardiac systems of mother and fetus. However, there has been no evidence of maternal–fetal heartbeat-to-heartbeat coordination, until now. The article by Van Leeuwen et al. (14) published in this issue of PNAS does just that: applying a novel concept from physics and nonlinear dynamics to their data, they uncover a hitherto-unknown phase synchronization between the individual heartbeats of mother and fetus—a marker of coupling between their autonomous cardiac systems despite continuous noisy fluctuations in the beat-to-beat intervals.

Using multichannel magnetocardiography to simultaneously record the magnetic fields generated during each maternal and fetal heartbeat at resting supine condition, Van Leeuwen et al. (14) derive time series of consecutive heartbeat intervals, and they discover epochs of synchronization where fetal heartbeats occur at the same instantaneous phases within each consecutive maternal heartbeat cycle—the first evidence of direct coupling mediated by the maternal cardiac activity. Such

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mother–fetus heartbeat phase synchronization at beat-to-beat time scales is rather surprising, given their autonomous central nervous systems and separate blood circulation (placental barrier). Various factors—including maternal stress and anxiety levels associated with release of glucocorticoids and corticosteroid hormones (15) (which easily pass through the placental membrane); activation of the maternal autonomous nervous system by increased levels of acetylcholine triggering excitatory actions and body movements (16); variations in catecholamine concentrations resulting in maternal vasoconstriction and consequent restriction of oxygen to the fetus (11, 12)—all suggest certain influence on the average fetal heart rate and heart rate variability, however, at time scales much larger than beat-to-beat intervals. Indeed, recent cross-correlation analyses failed to identify a beat-to-beat association between maternal and fetal heart rate (17). Then, how did Van Leeuwen et al. succeed in identifying patterns of maternal and fetal heartbeat synchronization?

They related the problem of identifying maternal–fetal heartbeat coupling to an intriguing nonlinear phenomenon called synchronization—the adjustment of rhythms of self-sustained oscillators because of their interaction (18). First described by Huygens in 1665, who observed that the oscillations of two pendulum clocks suspended from the same wooden beam coincided perfectly due to their weak interaction mediated through the beam, synchronization has since been found in various physical and biological systems—from clocks and musical instruments, to cooperative behavior of crickets and fireflies, to circadian cycles and synchronous firing of neurons (18). Notably, a very weak, often imperceptible, interaction between oscillatory systems can cause a qualitative transition: an object adjusts its rhythm in conformity with the rhythm of other objects. For two weakly coupled oscillatory systems with regular dynamics and nonidentical frequencies, synchronization results in "locking" of their frequencies f_i (i.e., $mf_1 - nf_2 = 0$, where m and n are integers) or of their respective phases ϕ_i (i.e., $m\phi_1 - n\phi_2 = const$, where $d\phi_i(t)/dt = 2\pi f_i$ and the ratios m:n correspond to different phase-synchronization patterns) (19). To identify and quantify the degree of coupling between oscillatory systems with noisy irregular or chaotic dynamics, where the amplitudes are not cross-correlated (and thus traditional cross-correlation methods do not work), a novel phase-synchronization approach has been recently developed (18, 20) and applied to several physiologic systems, including cardiorespiratory synchronization in healthy adults at rest (21) and its change across sleep stages (22); synchronous activation of cortical centers during epileptic seizures (23); and cerebral autoregulation in subjects after ischemic stroke (24). The study of Van Leeuwen et al. (14) goes further to discover phase synchronization between autonomous physiologic systems of different organisms, the maternal and fetal heart.

The specific mechanism leading to maternal–fetal heartbeat phase synchronization remains elusive, and two hypotheses for pathways mediating this

Author contributions: P.Ch.I., Q.D.Y.M, and R.P.B. wrote the paper.

The authors declare no conflict of interest.

See companion article on page 13661.

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interaction are plausible: (*i*) the oscillatory rhythm of maternal respiration acts as a common driving force and influences simultaneously both maternal and fetal heart rates, leading to an apparent maternal–fetal heartbeat synchronization; (*ii*) the maternal cardiac system has a direct detuning effect on the fetal heart rhythm.

At normal breathing rates, the respiratory rhythm leads to cyclical cardiac variations where the heart rate increases during inhalation and decreases with exhalation, a phenomenon called respiratory sinus arrhythmia (RSA) (16). RSA, a noninvasive measure of parasympathetic tone reflected in high-frequency heart rate oscillations, is increasingly pronounced (i.e., larger amplitude of heart rate variation) with decreasing respiratory rates (16). Further, lower respiratory rates are associated with a higher degree (longer epochs) of cardiorespiratory phase synchronization in normal subjects (25), suggesting increased maternal cardiorespiratory synchronization. In parallel, lung tidal volume and chest and abdomen movement are larger at lower breathing frequencies, raising the possibility for increased mechanical stimulation of the uterus, and thus driving the fetal heart rate to phase-synchronize with the maternal respiration and correspondingly with the maternal heart rate. Performing measurements over a range of maternal breathing frequencies, Van Leeuwen et al. (14) show the opposite: significantly higher maternal–fetal heartbeat synchronization at higher respiratory rates, indicating that maternal–fetal cardiac coupling may not be mediated by maternal respiration.

An intriguing alternative hypothesis suggested by Van Leeuwen et al. (14) is that maternal–fetal cardiac coupling is mediated by acoustic stimuli of maternal heartbeat and vessel pulsation perceived by the fetal auditory system. These stimuli may act as an external forcing rhythm to entrain the fetal heartbeat to the beat of the mother. Indeed, experiments have demonstrated that the heartbeat of healthy subjects at rest synchronizes with periodic sequences of weak external sound pulses (19). However, this could not quite explain the findings by Van Leeuwen et al. of a higher degree of synchronization at higher respiratory rates, because both maternal and fetal mean heart rate remain practically unchanged with increased frequency of paced maternal respiration (ref. 16 and table 1 in ref. 14). A possible explanation for the increase in maternal–fetal heartbeat synchronization at higher maternal respiratory rates is the observed lower standard deviation of the maternal heartbeat increments (ref. 16 and table 1 in ref. 14), leading to a more regular maternal heartbeat at higher respiratory rates, thus generating more regular acoustic stimuli with which the fetal heartbeat can better synchronize (25). This argument is further supported by the observation that the standard deviation of the fetal heartbeat increments significantly drops at a high maternal respiratory rate when the maternal–fetal phase synchronization is most pronounced (14). Whether such an acoustic mechanism is indeed responsible for the maternal–fetal heart rate coupling remains to be further investigated, given that the gradual increase in synchronization with an increasing maternal respiratory rate is not paralleled by a simultaneous decrease in the standard deviation of the fetal heartbeat increments.

The work by Van Leeuwen et al. (14) is a significant step toward a better understanding of the complexity of maternal–fetal interaction at the integrated system level. Elucidating the mechanistic pathways underlying this interaction remains a major challenge, as these pathways involve multiple contributing factors, from the biochemical to the system level, acting through various feedback loops and over a range of time scales. Further investigations are needed to clarify the physiological significance of the maternal–fetal heart rate phase synchronization at beat-to-beat time scales, and whether mother and child benefit from this specific interaction. As the complexity in fetal heartbeat fluctuations increases with gestation age, it is conceivable that maternal–fetal cardiac coupling may also evolve with maturation. Quantifying the degree of this coupling for different gestation age may prove instrumental in deriving novel clinical markers of healthy prenatal development and pathological deviation.

ACKNOWLEDGMENTS. This work was supported by Grant P06-FQM1858 from the Spanish Junta de Andalucia.

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